REMARKS

Claims 19-29 are pending in the present application. Claims 1-18 have been cancelled. Support for new claims 19-29 may be found at least as follows. New claims 19 and 20 correspond to original claims 1 and 2. Support for new claim 21 may be found on page 30, line 22 through page 33, line 4. New claims 22 and 23 correspond to original claims 4 and 5. Support for new claim 24 may be found in original claim 10 and on page 79, lines 4-8 and page 155, lines 5-9 of the specification. Support for new claim 25 may be found in original claim 11 and on page 79, lines 4-8 and page 155, lines 5-9 of the specification. Support for new claim 25 may be found in original claim 12 and on page 144, line 8 though page 157, line 16, particularly at page 152, line 17 through page 157, line 16. New claims 27-29 correspond respectively to original claims 14-16 with the dependency correctly recited for the new claim numbers. New claims 19-29 in no way add new matter to the specification. As such, entry and consideration thereof is respectfully requested.

Restriction of the claims

The Examiner has required election in the present application between:

Group I, claims 1-5, in part, drawn to compounds, composition and method of use and method of making compounds of

formula (I), wherein A is a 6-membered heterocycle, B is a single bond, X is -CH2, Y is oxygen, m is 0, l is 1, z is -CO-, T is SO2, and Z is phenyl or naphthalene;

Group II, claims 6, 7, and 9, in part, drawn to compounds, compositions, methods of using and methods making compounds of formulae V, VI, and Ia'; and

Group III, claims 8, 10, 11, 12, in part, drawn to compounds of formulae Ik, I'', I''' and I'.

Applicants traverse this restriction as being improper and withdrawal thereof is respectfully requested.

On page 2 of the restriction requirement issued on September 12, 2003, the Examiner designates the invention of Group I, in part, as being:

Claims 1-5 drawn to compounds of formula(I) wherein "X=-CH_2-". However, Claim 1 does not recite that "X" "-CH_2-" but rather that

> "X is a nitrogen atom or a methine group optionally substituted with a group A'-B'-(wherein A' represents a group selected from those defined for A, and B' represents a group selected from those defined for B)."

Thus, "X=-CH_2-" as listed by the Examiner, is not recited in Claim 1 since "X=-CH_2-" is not a methine. If X is designated as "-CH_2-" in formula (I) the invention cannot possibly be achieved. Accordingly, Applicants believe that the claims should be re-grouped.

Newly added claims 19-29 more clearly recite the unity of invention possessed by the presently claimed subject matter. The present specification provides over 700 examples on pages 164 to 297, which fall under the claimed structure of independent claim 1. In addition, the original claims that did not define the invention by any structural formula (claims 13, 17 and 18) or original claims that recited intermediates suitable for preparing tricyclic compounds having spiro union (claims 6, 7, 8 and 9) have been deleted.

As stated by MPEP §803.02, "it is improper for the Office to refuse to examine that which applicants regard as their invention unless the subject matter in a claim lacks unity of invention of invention. *In re Harnisch*, 206 USPQ 300 (CCPA 1980)...unity of invention exists where compounds included within a Markush group (1) share a common utility and (2) share a substantial structural feature disclosed as being essential to that utility." Both are present in the present case, i.e. all of the claimed compounds have a common utility as pharmaceutical compounds having anticoagulation activity and a common structural feature of tricyclic compounds having spiro union, so restriction is entirely without basis and improper.

As noted, newly added claims 19-29 are all drawn to tricyclic compounds having spiro union, which are represented by the single chemical formula. Applicants believe the tricyclic compounds

having spiro union represented by the single formula and having a common utility meet the requirements for being met the unity of the invention.

Applicants' position is further supported by the fact that the claims corresponding to present claims 19-29 have been found allowable and having unity of invention in the corresponding European application.

The present invention is based on the discovery that the compounds of formula (I) having the indicated spiro skeleton have extremely potent FXa inhibitory activity, as described on page 11 lines 3 to 9 of the specification. The compounds of the invention have a novel tricyclic structure having a spiro union, e.g., 1,4-diaza-7-oxa—1'-spiro[bicyclo [4.3.0] nonane-8, 4'-piperidin] ring, 1,4,7-triaza-spiro [bicyclo [4.3.0] nonane-8, 4' -piperidin] ring or the like.

The novel structure of the invention is very important. As discussed in the Examples describing the X-ray crystallography analysis, found on line 15 of page 350 through line 9 of page 358 in the specification and from line 23 of page 357 to line 9 of page 358, the tricyclic compounds of the invention, including the novel spiro union, contributed to having been able to find the novel pharmacophore of the invention, which had not been reported for already-known Fxa inhibiting compounds, by fixing the tricyclic three-dimensional conformation to specific coordinate positions.

As discussed on page 9, lines 1-17 of the specification, the present invention determined, for the first time, what kind of structure should be studied for developing different types of FXa inhibitors. In addition, as a result of the present work, the demerits of already-known FXa inhibitors such as DX-9065a and FX-2212a, whose availability with oral administration is insufficient and and which have side effects from amidino groups or guanidine groups, were overcome. The information obtained from the present work regarding the interactions between FXa and FXa-inhibitory compounds based on the data of the crystal structure of the complex between the FXa and the FXa-inhibitory compounds of the invention is ground-breaking and extremely important in the field of FXa inhibitors.

As described in the sections entitled "Results of the analysis" on page 357 of the specification and "Measurement of the activity" on pages 357-358 of the specification, compounds that satisfy all the criteria discussed in Aspect 17-b on pages 80-82 of the specification have full FXa inhibitory activity. The criteria of Aspect 17-b are also described in Aspect 10 on pages 72-76. The compounds of the invention have at least the common structural requirements of having at least the tricyclic structure having a spiro union of formula (I).

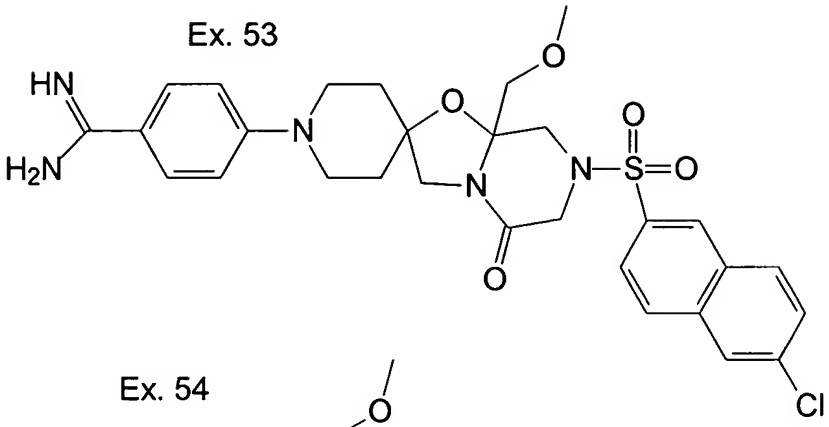
From the designation of the Groups by the Examiner, it appears that the Examiner believes the substituents A and B in formula (I)

of Claim 1 are broad enough to require restriction. However, as explained below, the scope of the invention encompassed by new claim 19, which corresponds to original claim 1, is reasonable and possesses unity of invention.

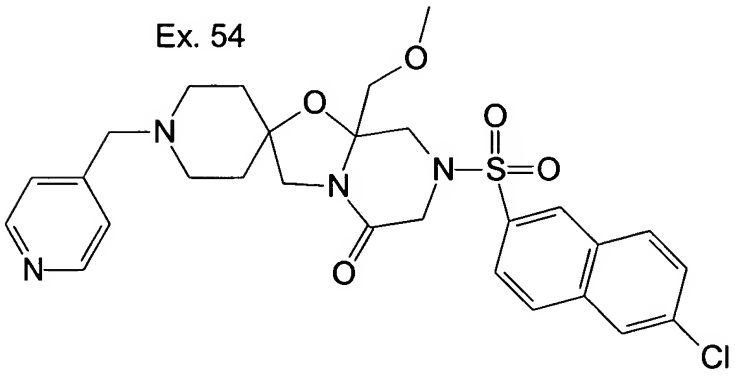
The Table below summarizes the results the anticoagulation activity of the compounds of Examples 53, 54 and 56. The specification fully describes the chemical name, chemical structure and synthesis of these compounds. In addition, the chemical structures for each compound in the Table are shown immediately following the Table.

Test compound	**Experiment 1**: Human FXa inhibitory action IC_{50} (nM)	**Experiment 2**: anticoagulant activity Concentration required to double coagulation time (μM)
Example 53	55.2	8.91
Example 54	135	10.3
Example 56	7.7	0.36

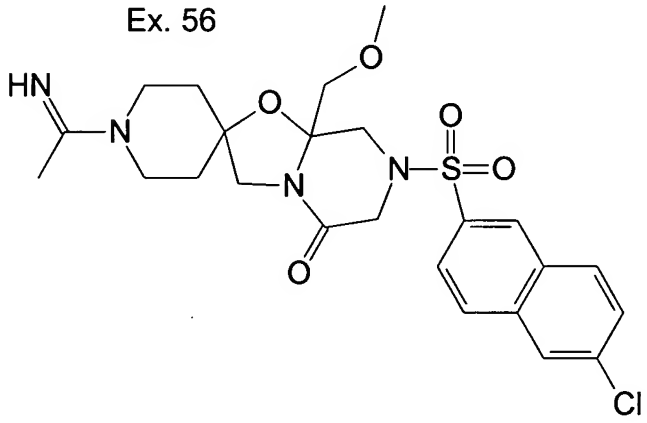
Ex. 53



Ex. 54



Ex. 56



The compound of Example 10 of Table 1, found on page 165 of the specification, has a 4-pyrimidinyl group "A", instead of a 4-pyridyl group. The compound of Example 23 of Table 2, found on

page 166 of the specification, has a 1-methyl-4-pyridinium group as "A", instead of a 4-pyridyl group.

With the compound of Example 53, A is a phenyl group bonded to amidino group (corresponding to recitation of a saturated or unsaturated five- or six-membered cyclic hydrocarbon group in claim 1) and B is a single bond (corresponding to recitation of a single bond in claim 1).

The compound of Example 54 is a compound wherein A is a 4-pyridyl group (corresponding to a saturated or unsaturated five- or six-membered heteocyclic hydrocarbon group of claim 1) and B is a methylene group (corresponding to a C1-2 alkylene group in claim 1).

The compound of Example 56 is a compound wherein A is an imidoyl group (corresponding to an imidoyl group in claim 1) and B is a single bond (corresponding to a single bond in claim 1).

From the test results shown in the Table above with the compounds of Examples 53, 54 and 56, the FXa inhibitory activity can be predicted for other compounds having A and B as defined in claim 1. As described on page 165, lines 3 to 7, FXa inhibitory activity of compounds of the present invention was measured with activities of 0.1 nM to 1 μM as IC_{50} values. Therefore, the compounds that are described above, and encompassed by claim 1, have full FXa inhibitory activity. Moreover, the compounds have a full pharmacological profile in measurements (in vitro) of anti-

coagulation activity. The experimental results shown above fully support the recited definition for A and B in formula (I) of claim 1 of the present invention, and as such, the definitions recited in Claim 1 are appropriate.

During an informal telephone discussion with the Examiner, which the Applicants' representative found very helpful, the Examiner indicated that he would be receptive to a suggested regrouping of the claims by Applicants. Applicants suggest that the subject matter disclosed in the specification might be grouped logically as follows.

Group	Category	New claims	Original claims and the grouping of the Examiner
I	Final compounds having tricyclic spiro union	19-23 24-26 27-29	1-5(Group VI) 10-12(Group III) 14-16(the portion of Group IV which relates to claims 10-12)
II	Intermediates compounds	None	6-9(Group II and Claim8)
III	pharmacophore not represented by any formulas	None	13,14-16(the portion of Group IV which relates to claim 13) 17-18(Group V)
IV	all others	None	Group I(there is not in the definition of the Invention)

All original claims pertaining to the subject matter of groups other than of Group I have been cancelled and have not been represented in new claims 19-29. New claims 19-29 are drawn solely

to tricyclic compounds having a spiro union. As such, claims of 19-29 are drawn to common subject matter having unity of invention.

As described in the International Preliminary Examination Report issued in PCT/JP00/04374 (corresponding International Application to the Application), a copy of which is attached,

<1> the invention relates to compounds which have a certain specified chemical structure and have Fxa inhibiting activity, pharmaceutical compositions including the same, a process for production thereof, and intermediates for the production thereof (see original Claims 1-12) and on the other hand

<2> the invention relates to compounds which inhibit FXa because of interactions with the S1 and the S3 pockets of FXa, and the method of prediction thereof (original Claims 13-18).

With the Claims relating to the above described group <1>, the inventive final compounds having a tricyclic spiro union are the compounds represented by formula (I) of original Claim 1, formula (I") of original Claim 10, formula (I''') of original Claim 11 and formula (I') of original Claim 12.

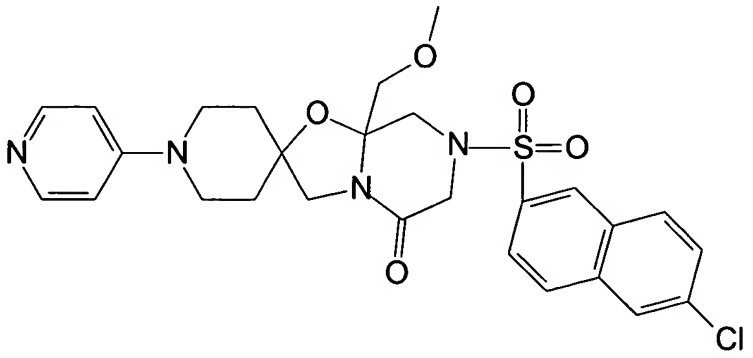
The compounds encompassed by original claims 6, 7 and 9 of <1> above, are intermediates for production of the inventive final compounds having the tricyclic spiro union of the invention. Thus, the intermediates are grouped herein by Applicants as a separate invention under practice before the USPTO (see the Grouping Chart on the previous page). For this reason, these compounds are not

included in newly presented claims 19-29. The compounds represented by formula (Ik) in original claim 8 are also intermediates for production of final compounds, as described on page 92 lines 10-23 in the specification.

In summary, the inventive final compounds of having a tricyclic spiro union are encompassed by new claims 19-29 and should be examined in one Group as the final product compound of the invention. The present invention provides over 700 examples on pages 164 to 297, which fall under the claimed structure. In addition, these compounds meet the requirements for unity of invention with the common structural element of the tricyclic spiro union and common utility as anticoagulation agents. As such, examination of new claims 19-29 is respectfully requested.

Election of species

The Examiner has further required that Applicants elect a single species to begin searching. Applicants elect, with traverse, the following compound of Example 1:



Applicants further request that should no prior art be found regarding the elected compound, the remaining compounds of claim 20 be rejoined and searched.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong (Reg. No. 40,069) at the telephone number of the undersigned below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
Gerald M. Murphy, Jr., #28,977

MaryAnne Armstrong, Ph.D., #40,069

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

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GMM/MAA:bmp

Attachments: English Translation of International Preliminary Examination report issued in PCT/JP00/04374